Remarks

Claims 38-73 were pending in the subject application. By this Amendment, claims 38, 43, 44, 46, 55-57, 65-67, 69, 72, and 73 have been amended, and new claims 74-87 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 38-87 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a Request for Continued Examination (RCE) under 37 C.F.R. §1.114 for the subject application. Also submitted herewith is an Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08 and copies of the references listed therein. The applicant respectfully requests that the references listed on the form PTO/SB/08 be considered and made of record in the subject application.

The applicant and the applicant's representative wish to thank Examiners Zara and McGarry for the courtesy of the telephonic interview conducted with the undersigned and Dr. William Kerr, the inventor of the claimed subject matter, on December 21, 2004, regarding the rejections under 35 U.S.C. §112, first paragraph. The remarks and amendments set forth herein are consistent with the substance of the interview and are believed to address the outstanding issues as discussed during the interview.

A Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures was attached to the outstanding Office Action and a copy of the Notice is attached herewith. A Submission of Sequence Listing under 37 C.F.R. §§1.821-1.825, including a sequence listing on paper and a computer readable format is attached.

By this Amendment, claims 38, 43, 44, 46, 55-57, 65-67, 69, 72, and 73 have been amended, and new claims 74-87 have been added. Claims 38, 46, 57, 67, and 69 have been amended to recite that the SHIP-1 mRNA is present in hematopoietic cells and the mammal is human or mouse. Support for these amendments can be found, for example, at page 2, lines 13-17, page 11, lines 3-5, and 31-34, and page 17, lines 1-3, of the specification. Support for the amendments to claims 43, 44, 55, 56, 65, 66, 72, and 73 can be found, for example, at page 7, lines 30-32, page 11, lines 31-34,

page 12, page 13, 1-17, page 14, lines 4-6, and page 16, lines 31-34, of the subject specification, and the claims as originally filed.

By this Amendment, new claims 74-87 have been added. Claims 74, 77, 80, 83, and 85 are directed to methods and compositions involving a nucleic acid molecule that hybridizes *in vivo* with SHIP-1 mRNA. Support for this aspect of the claims can be found, for example, at page 5, lines 33-34, page 6, lines 26-27, and page 11, lines 25-26, which indicate that, in a preferred embodiment, the substance that inhibits SHIP function is a nucleic acid that hybridized to a SHIP mRNA; page 9, lines 14-15, which indicates that the agent used to inhibit SHIP function may be a means for interfering with transcription and/or translation of SHIP RNA; and page 15, lines 33-34, of the specification, which indicates that polynucleotide DNA can direct production of RNA or a polypeptide that inhibits SHIP activity. Claims 74, 77, 80, 83, and 85 recite that the SHIP-1 mRNA is present in human or mouse hematopoietic cells. Support for this aspect of the claims can be found, for example, at page 11, lines 3-5 and 31-34, and page 17, lines 19-21, of the subject specification. Claims 74, 77, 80, 83, and 85 recite that the nucleic acid molecule hybridizes *in vitro* with the human or mouse SHIP-1 mRNA under conditions of stringency. Support for this aspect of the claims can be found, for example, at page 15, lines 15-28, of the subject specification. Claims 75, 78, 81, 84, and 86 recite that the nucleic acid molecule is an RNA molecule. Support for this aspect of the claims can be found, for example, at page 14, line 7, which indicates that the nucleic acid may be DNA or RNA, and page 15, lines 33-34, which indicates that the DNA can direct production of RNA or a polypeptide that inhibits SHIP activity.

Claims 38-73 have been rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description. The applicant traverses and respectfully submits that the subject specification provides a sufficient written description of the claimed invention.

The Office Action indicates that the specification does not provide an adequate written description of the genus claimed. Specifically, the Office Action states that nucleotide sequences from two mammalian species (human and mouse), which were known in the art at the application was filed, are not representative of the various sequences encompassed by the genus comprising any mammalian SHIP-1 mRNA. By this Amendment, independent claims 38, 46, 57, 67, and 69 have been amended to recite that the interfering RNA is specific for SHIP-1 mRNA present in

hematopoietic cells of the mammal, and to recite that the mammal is a human or mouse. New independent claims 74, 77, 80, 83, and 86 recite a nucleic acid molecule that hybridizes *in vivo* with SHIP-1 mRNA present in human or mouse hematopoietic cells. As indicated at page 2, lines 13-17, and page 11, lines 3-5, of the specification, and page 508, column 2, of Exhibit B (Rohrschneider *et al.*), SHIP-1 is expressed in hematopoietic cells.

Submitted herewith for the Examiner's consideration is a Declaration under 37 C.F.R. §1.132 by Dr. Kerr, including Exhibits A-C. Exhibit A is mammalian orthology data for SHIP-1 obtained from the National Center for Biotechnology Information's (NCBI) Homologene database, which is a publicly available system for automated detection of homologs among the annotated genes of several completely sequenced eukaryotic genomes, and is utilized by those of ordinary skill in the art. Exhibit A includes a table of pair wise alignment scores, showing levels of SHIP-1 homology among humans, mice, rats, and a potential chimpanzee SHIP-1 sequence. As shown in Exhibit A, each sequence has the SHIP-1 enzymatic domain (inositol 5'-phosphatase), and the degree of nucleotide homology between human SHIP-1 and mouse and rat SHIP-1 is over 85%. Furthermore, Dr. Kerr indicates

> [a]lthough the potential chimpanzee orthologue is shown on the database to lack a detectable amino-terminal src-homology domain (SH2), it is noteworthy that there is nonetheless 97% nucleotide homology between human SHIP-1 and the chimpanzee sequence. Furthermore, mice and humans are believed to have the same five SHIP-1 protein isoforms. There would be no difficulty in identifying target mRNA sequences shared by all known hematopoietic SHIP-1 isoforms in humans and mice, due to the extensive amount of sequence overlap between the isoforms (see Figure 2A of Rohrschneider *et al.*, *Genes & Development*, 2000, 14:505-520, the full text of which is submitted herewith as Exhibit B). Kerr Declaration, section 4, pages 2-3.

It should also be appreciated that the SHIP-1 enzymatic domain, "which one of ordinary skill in the art would likely consider the starting point for selecting any inhibitory hybridizing nucleic acid molecule for SHIP-1, is very high in all five isoforms" (Kerr Declaration, page 3, lines 3-5).

Based on the high degree of homology between known mammalian SHIP-1 orthologues, and the high degree of conservation between SHIP-1 isoforms, the applicant submits that the subject specification provides an adequate written description of human and mouse SHIP-1 mRNA, as well as mammalian SHIP-1 mRNA. Having the sequence of the target gene (SHIP-1) and knowledge of its structure, including its relevant isoforms, at the time of filing, one skilled in the art could readily

envision target nucleic acid sequences within and along the recipient mammal's mRNA. Due to the certainty of the genetic code and nucleotide complementarity, nucleic acid molecules likely to hybridize with SHIP-1 mRNA and interfere with its expression could then be determined. Accordingly, the teaching of the subject specification and knowledge of the sequence and structure of the SHIP-1 gene provides sufficient structural and functional correlates to describe the genus of target mRNA and corresponding interfering RNA.

Recognizing that the state of the art has sufficiently developed, the Federal Circuit has held that "the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it ... one of ordinary skill in the art at the time the ... application was filed may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or rendered obvious". *In re Wallach*, 71 USPQ2d 1939; 378 F.3d 1330 (CAFC 2004). The Court also cited the Patent Office's Manual of Patent Examining Procedure (MPEP), which states:

> Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. For example, in the molecular biology arts, if an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence. Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full genus of nucleic acids encoding a given amino acid sequence, but not necessarily any particular species. MPEP §2163.II.A.3.a.ii. (8th ed., rev. 2, 2001 and May, 2004).

"Moreover, we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it." *In re Wallach*, at 1942.

Thus, the applicant submits that the subject specification contains sufficient disclosure to convey to one of ordinary skill in the art that the applicant had possession of the concept of what is claimed, which is all that is necessary to satisfy the written description requirement of 35 U.S.C.

§112, first paragraph. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 38-66 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicant respectfully traverses and submits that the claims are fully enabled by the subject specification.

The Office Action indicates that, in order for the full scope of the instant invention to be enabled, the results obtained using ablation experiments (in an ablated mouse model) cannot be substituted for treatment effects in any mammal using interfering RNA targeting any mammalian SHIP-1 mRNA. As indicated above, by this Amendment, independent claims 38, 46, 57, 67, and 69 have been amended to recite that the interfering RNA is specific for SHIP-1 mRNA present in hematopoietic cells of the mammal, and to recite that the mammal is a human or mouse. New independent claims 74, 77, 80, 83, and 86 recite a nucleic acid molecule that hybridizes *in vivo* with SHIP-1 mRNA present in human or mouse hematopoietic cells. The sequences of the human and mouse SHIP-1 gene were known at the time the subject application was filed. Furthermore, as indicated above, there is a high degree of homology between known mammalian SHIP-1 orthologues, and a high degree of conservation between SHIP-1 isoforms. Having the sequence of the target gene, SHIP-1, and knowledge of the gene's structure, one skilled in the art could readily envision target nucleotide sequences within the recipient mammal's mRNA. There would be no difficulty in identifying target mRNA sequences shared by all known hematopoietic SHIP-1 isoforms in humans and mice, due to the extensive amount of sequence overlap between the isoforms. Due to nucleotide complementarity, nucleic acid molecules likely to hybridize with SHIP-1 mRNA and interfere with its expression could then be determined without resort to undue experimentation. Figure A of Exhibit G and Exhibit H of Dr. Kerr's previous Declaration dated July 16, 2004, which was submitted in response to the previous Office Action, showed that C57BL6/J mice injected i.p. on days 1, 2, and 3 with a SHIP-1 shRNA vector complexed with the cationic lipid DOTAP resulted in significant suppression of all detectable SHIP-1 isoforms in the spleen.

The Office Action indicates "[i]t is still highly unpredictable that complete ablation will be obtained using these inhibitory molecules, and a measure of the extent of target gene inhibition

required to achieve this treatment effect (observed in an ablated mouse model) must be determined empirically and therefore requires undue experimentation" (page 7 of Office Action).

Referring to Dr. Kerr's previous Declaration dated July 16, 2004, Exhibit I and Figure B of Exhibit G showed that pooled siRNA molecules complexed with DOTAP and injected i.v. into C57BL6/J mice resulted in partial suppression of SHIP-1 expression in peripheral mononuclear cells (PBMC) and a significant increase in Mac+Gr1-monocytes and circulating Mac1+GR1+ cells (myeloid suppressor cells), compared to controls. These results show that SHIP-1-specific interfering RNA can have profound physiological effects in a rapid fashion, even when complete knockdown is not achieved. As indicated at page 11, lines 10-34, page 12, and page16, lines 1-18 and 31-34, of the subject specification, various viral and non-viral vectors such as polycationic molecules may be utilized to deliver nucleotides. Column 17 of U.S. Patent No. 6,025,198, which was cited by the Examiner in the previous Office Action, indicates that cationic liposomes may be used to deliver antisense oligonucleotides to inhibit expression of SHIP-2. DOTAP, which was the delivery vehicle utilized by Dr. Kerr in this experiment, has been used for gene delivery to mammalian cells *in vitro* and *in vivo* for some time (see, for example, Porteous D.J. *et al.*, "Evidence for safety and efficacy of DOTAP cationic liposome mediated CFTR gene transfer to the nasal epithelium of patients with cystic fibrosis", *Gene Ther.*, 1997, Mar., 4(3):210-218; Song Y.K. *et al.*, "Characterization of cationic liposome-mediated gene transfer *in vivo* by intravenous administration", *Hum. Gene Ther.*, 1997, Sept., 8(13):1585-1594).

Referring now to the Declaration dated January 18, 2005, which is submitted herewith, Dr. Kerr indicates that "... even partial induction of SHIP-1 deficiency *in vivo* can increase the representation of cells capable of suppressing allogeneic T cell priming. A reduced allogeneic T cell response is considered by those in the field as a key determinant to successful engraftment" (Kerr Declaration, page 5, section 8). Figures A-C of Exhibit C, which accompanies Dr. Kerr's Declaration, show that induction of SHIP-1 deletion in the adult MXCreSHIPflox/- mice increases MSC numbers in the lymph node (LN) and spleens of mice, and leads to compromised priming of allogeneic T cells. This does not require complete ablation of SHIP-1 expression, as mice with partial SHIP-1 ablation also show significantly reducing priming of allogeneic T cells. As indicated by Dr. Kerr in his Declaration, "the MXCre mouse represents a stringent model for assessment of

altered SHIP-1 function, and is recognized by those in the field as a valid tool for determining the physiological effects of endogenous gene ablation *in vivo*" (Kerr Declaration, page 5, section 8). Furthermore, Figures D and E of Exhibit C, which accompanies Dr. Kerr's Declaration, show that SHIPflox/- mice with myeloid-specific expression of Cre (LysCre) have a significant increase in MSC that leads to profound suppression of allogeneic T cell priming. "Again, only a partial deletion of SHIP-1 in the myeloid lineage is required to achieve significant suppression of allogenic T cell responses, which mediate GVHD and organ graft rejection ... [t]hus, this physiologic response is clinically favorable and reasonably correlates with a therapeutic benefit in mediating GVHD and organ graft rejection" (Kerr Declaration, page 5, section 8).

The applicant respectfully submits that, in view of the disclosure of the subject specification as originally filed, and in view of the experimental results developed using those techniques which are described in the specification and known to those of ordinary skill in the art, compositions and methods for reducing SHIP-1 expression using interfering RNA, as currently recited in the claims, are fully enabled.

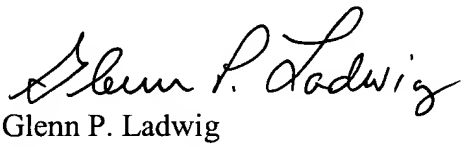
Accordingly, the applicant respectfully submits that, given the teaching of the specification and the state of the art in gene suppression using interfering RNA, one of ordinary skill in the art could carry out the claimed methods without the need for undue experimentation. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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